REMARKS

Following entry of the above amendment, claims 15-17 and 25 will be pending in the present application. Claims 14 and 19-22 have been cancelled without prejudice to or disclaimer of the subject matter contained therein. Claims 19-22 are cancelled due to the restriction requirement. Claim 15 has been rewritten in independent form and has further been amended to recite that the cancer to be treated is breast cancer. Support for the amendment can be found in the specification and claims as filed including, for example, in paragraph 118 of the US patent application publication. Claims 15-17 and 25 have been amended to increase clarity and consistency. The title has been amended in response to a request by the Examiner. No new matter has been added by way of amendment.

The Information Disclosure Statement

According to the Office Action, the Information Disclosure Statement filed October 16, 2006 has not been considered because reference 3 was not found in the file. Apparently, this reference was not transmitted to the USPTO by the ISA. Applicants submit herewith a new Information Disclosure Statement citing this reference and a copy of the cited reference.

Specification

The Examiner has objected to the title of the invention on the grounds that it is not sufficiently descriptive. The title has been amended in accordance with the Examiner's comments.

The Rejection Under 35 U.S.C. § 112, Second Paragraph, Should be Withdrawn

Claims 14-16 have been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that the phrase "physiologically functional derivatives" is unclear. Claim 14 has been cancelled, rendering the rejection of this claim moot. Applicants respectfully disagree with the rejection as applied to claims 15 and 16. The meaning of this phrase is well known to those of skill in the art. See, for example, paragraph 87 of the published US patent application and the references cited therein. Nevertheless, in order to expedite prosecution, this phrase has been deleted from claim 15, thereby obviating the rejection.

The Rejection under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 14-17 and 25 have been rejected under 35 U.S.C. § 103(a) on the grounds that they are unpatentable over Boloor *et al.* (WO02059110) and Ciardiello *et al.* in view of Rusnak *et al.* Claim 14 has been cancelled, rendering the rejection of this claim moot. The rejection is respectfully traversed as applied to claims 15-17 and 25 for the reasons described below.

The Examiner states that it would be *prima facie* obvious to one of ordinary skill in the art to treat cancer with GW2016 (taught by Rusnak *et al.*) in combination with a compound of Formula I because both compounds were known in the art to be capable of treating cancer. However, the factual finding presented in the Office Action is insufficient to establish a *prima facie* case of obviousness. While one of ordinary skill in the art might be motivated to test various combinations of anti-cancer agents in a method of treating cancer, it is not possible to predict *a priori* which combinations will be beneficial to patients. For example, the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib has been tested in clinical trials for treatment of non-small-cell lung cancer in combination with carboplatin but the combination showed no benefit in comparison with monotherapy. See, for example, Herbst *et al.* (2004) Journal of Clinical Oncology 22:785-94, provided herewith as **Appendix A** for the convenience of the Examiner. In another clinical trial, a combination of gefitinib with gemcitabine and cisplatin was shown to have no benefits in comparison with the gemcitabine/cisplatin combination alone. See, for example, Giaccone *et al.* (2004) Journal of Clinical Oncology 22:777-84, provided herewith as **Appendix B** for the convenience of the Examiner. Similarly, clinical data has shown that the anti-cancer agent erlotinib does not offer a benefit when combined with cisplatin and gemcitabine (Gatzemeier *et al.* (2007) Journal of Clinical Oncology 25:1545-1552, provided herewith as **Appendix C** for the convenience of the Examiner) or with carboplatin and paclitaxel (Herbst *et al.* (2005) Journal of Clinical Oncology 23:5892-99, provided herewith as **Appendix D** for the convenience of the Examiner). Like GW2016, both gefitinib and erlotinib are quinazolinamines that target the epidermal growth factor receptor (EGFR) tyrosine kinase. These examples illustrate that while it might be obvious to try various anti-

cancer agents in combination for the treatment of cancer, it is not possible to predict which particular combinations will offer therapeutic advantages in a particular type of cancer in comparison with treatment with the corresponding single agents alone. Accordingly, in the absence of experimental evidence, one of skill in the art would not have a reasonable expectation that any particular combination would be successful.

Even if the Office Action had established a *prima facie* showing of obviousness for the invention recited in claims 15-17 and 25, there is sufficient evidence to rebut such a showing. Recently, preliminary results of a phase II clinical trial comparing the results of treating of breast cancer with GW2016 alone with the results of treating breast cancer with GW2016 combined with a compound of Formula I have been reported. See, for example, Slamon *et al.* (2008) *J. Clin. Oncol.* 26 (May 20 suppl; abstr 1016) and the associated slide presentation from the American Society of Clinical Oncology Meeting in May of 2008, a copy of which is provided herewith for the convenience of the Examiner as **Appendix E**. In this phase II trial, breast cancer patients were treated with either GW2016 (lapatinib) alone at a dose of 1500 mg per day or a combination of a lower dose of lapatinib (1000 mg per day) and a compound of Formula (I) (pazopanib; 800 mg per day). The response rate at week 12 was 44.9% with the combination and 28.8% with the lapatinib monotherapy according to the investigator's assessment, and 36.2% with the combination and 22.2% with the monotherapy according to an independent assessment. See slide 12 of the slide set. In addition, patients treated with the combination showed an improved rate of progression-free survival during the 12-week treatment period in comparison with patients treated with lapatinib monotherapy. See slide 11 of the slide set. Thus, the preliminary results of this clinical trial demonstrate that treatment of breast cancer with a reduced dose of lapatinib (1000 mg/day) combined with pazopanib at 800 mg/day offers therapeutic advantages when compared with treatment with a higher dose (1500 mg per day) of lapatinib alone.

In view of the above arguments, all grounds for rejection under 35 U.S.C. § 103 have been overcome. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

Applicants believe that all claims are in condition for allowance and such action is respectfully requested. Applicants believe that no other fees are due in connection with the filing of this paper other than those specifically authorized herewith.

Should any other fees be deemed necessary to effect the timely filing of this paper, the Commissioner is hereby authorized to charge such fees to Deposit Account No. 07-1392. If the Examiner has any outstanding issues with the pending claims, she is encouraged to telephone the undersigned at (919) 483-1467 for expeditious handling.

Respectfully submitted,

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Date: 8/26/2008

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